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Abstract:

This report describes initial progress in developing a biophysical description of the electrical events surrounding hormone release in pituitary cells. Utilizing a model based on a membrane capacitance shunted by potassium and calcium channels, we are developing a computer program that will simulate the dynamic response of the transmembrane potential of GH3 cells in response to thyrotropia-releasing hormone (TR4). When available, we are using published channel models of potassium and calcium channels. In parallel, we are persuing a phase-plane description of the electrical properties. These models and analyses will be used to investigate the effect of temperature on membrane action potentials.

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Annual Report: C. Frank Starmer, Ph.D.
Duke University Medical Center
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Models of Excitation-Secretion Coupling in Pituitary Cells

The focus of this research is to develop a biophysical description of the electrical events surrounding hormone release in pituitary cells, using observations derived from GH3 cells. In contrast to biophysical processes that operate at a single operating point and produce a continuous output of product, excitable cells in neural and cardiac systems appear to operate on a pulsed basis. For instance electrical activity in excitable cells is not represented by a slowly fluctuating membrane potential, but rather consists of bursts of action potentials. These potentials reflect the movement of charged ions across the cell membrane. Some ion movement appears primarily related to maintenance of the cell's membrane potential (Na^+) while other ions (K^+ and Ca^{++}) act as second messengers by activating other biochemical processes. The modeling of pulse-like systems has received little attention compared with continuous systems due to the perceived complexity in describing pulsatile phenomena.

Our work has focused on capturing the essential biophysical elements of these processes and developing mathematical models in order both to explore potential relationships between membrane electrical activity and cellular excitation and to plan experiments focused on postulated cellular mechanisms. In contrast to the work of Hodgkin and Huxley where channel activity was characterized by gating parameters

that describe the variation of total membrane conductance as a function of time, we have focused on models of channel activity that preserve the conductance properties at the single channel level. This provides a path for describing candidate mechanisms of interaction between ligands and specific channel conformations. For instance, we have been able to show that local anesthetics, antiarrhythmic and anticonvulsant agents bind to sodium, potassium and calcium channels in a manner consistent with traditional hormone-receptor interactions, that is with fixed affinity. However, drug binding of these agents to ion channel receptors is related to the frequency of electrical excitation of a cell. This process differs from traditional ligand receptor binding in that the binding site appears to only transiently be available or accessible. By assuming no latency in single channel conformation changes induced by stimulation, we were able to prove that results derived from the Hodgkin-Huxley model (as well as other gating models) are equivalent to results derived from a single channel model where the dwell time of the channel in its excited conformation was considered constant and equivalent to the mean dwell time of a stochastically operating channel (where the dwell time is exponentially distributed). The binding reaction, R + D <---> RD (R = receptor, D = drug, RD = drug-receptor complex) thus can describe binding to a periodically accessible binding site by considering the binding rate to switch between O for the resting channel to some non-zero value for the excited channel.

Approaching the characterization of pulsed neurotransmitter release with the same strategy has led to similar results. Here, instead of considering the channel binding site to

switch between accessible and inaccessible conformations, we have considered the hormone or neurotransmitter to be transiently available. In studies of stimulus induced transmitter release at the frog neuromuscular functions, Magleby and Zengel (J. Gen. Physiol. 80:613-638, 1982) found progressive increase in the amplitude of successive excitatory post-synaptic potentials during repetitive stimulation. By assuming a fixed amount of transmitter release with each stimulus pulse, we showed (Biometrics 44:549-559, 1988) that the pattern of post-synaptic potentials should be exponential with the rate directly proportional to the stimulus frequency. Furthermore, we showed that with random stimulation where the interstimulus intervals are exponentially distributed, the steady state amplitude of the excitatory post-synaptic potential should be related to the mean interstimulus interval.

With these results, we have approached developing a model of the electrical activity of the GH3 cell and its response to excitatory hormones. Our approach is to utilize the Hodgkin-Huxley view of a membrane patch as a membrane capacitance shunted by channels exhibiting different ion selectivities. Thus the central equation for describing the membrane potential is derived from a balance of the capacitive and ionic currents as

$$C_m \frac{dv}{dt} + I_K + I_{Ca} = 0$$

For the potassium currents, we assume two major classes of channels: a Ca^{++} activated K current and a voltage dependent K current. Further we assume that the stimulating hormone,

TRH, is coupled to the ionic channel system either directly through a receptor activated channel or through some sort of intermediate such as a G protein. As a starting point, we are following the approach of Rinzel (Biop. J. 54:411-425, 1988) and Chay (Biop. J. 42:181-190, 1983) and their model of electrical bursting activity in pancreatic β cells. The detailed mathematical model and computer programs for simulating cellular electrical properties will be completed during this year.

Finally, we have invested a small effort in correlating our work with that of models developed within the neural net community. The neural net models to date are rather nonbiological, but they do exhibit interesting behavior. Our idea is that in scaling hypotheses and models of cellular communication (either via electrical or hormonal excitation) from the single cell level to the multiple cellular level, it may be important to refine existing neural models to conform more closely with biological reality. Perhaps insights gathered through this research will aid in modeling the interconnections in neural nets. It would then be interesting to explore neural nets where connections between network components reflect similar feed-forward and feedback properties observed in biological preparations.

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